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FILE 'HOME' ENTERED AT 14:07:02 ON 11 JUN 2004

=> file medline caplus biosis embase scisearch agricola

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 14:07:30 ON 11 JUN 2004

FILE 'CAPLUS' ENTERED AT 14:07:30 ON 11 JUN 2004
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FILE 'BIOSIS' ENTERED AT 14:07:30 ON 11 JUN 2004

FILE 'EMBASE' ENTERED AT 14:07:30 ON 11 JUN 2004

FILE 'SCISEARCH' ENTERED AT 14:07:30 ON 11 JUN 2004

FILE 'AGRICOLA' ENTERED AT 14:07:30 ON 11 JUN 2004

=> s cyclic (p) hexapeptide
L1 2429 CYCLIC (P) HEXAPEPTIDE

=> s cyclohexapeptid?
L2 432 CYCLOHEXAPEPTID?

=> s l1 or l2
L3 2707 L1 OR L2

=> s propanolamine
L4 9770 PROPANOLAMINE

=> s l3 (p) l4
L5 5 L3 (P) L4

=> duplicate remove l5
DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L5
L6 4 DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)

=> d l6 1-4 ibib abs

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 1999:518280 CAPLUS
DOCUMENT NUMBER: 131:144854
TITLE: Preparation of **cyclohexapeptidyl propanolamine** compounds as antibiotics
INVENTOR(S): Hammond, Milton L.; Zambias, Robert A.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 771,017, abandoned.
CODEN: USXXAM

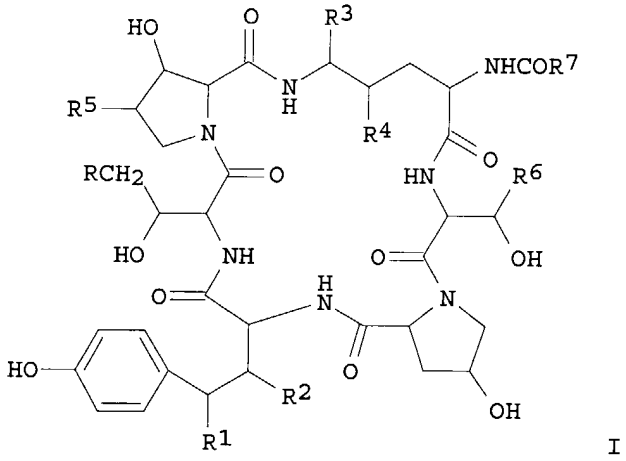
cyclohexypeptide-1

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5939384	A	19990817	US 1992-936561	19920903
CA 2079171	AA	19930402	CA 1992-2079171	19920925
CA 2079171	C	20001003		
EP 535959	A1	19930407	EP 1992-308974	19921001
EP 535959	B1	19970115		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 06234795	A2	19940823	JP 1992-263719	19921001
JP 07121958	B4	19951225		
AT 147757	E	19970215	AT 1992-308974	19921001
ES 2098455	T3	19970501	ES 1992-308974	19921001

PRIORITY APPLN. INFO.: US 1991-771017 B2 19911001
US 1992-936561 A 19920903

OTHER SOURCE(S): MARPAT 131:144854
GI



I

AB Title compds. I [R = CH2NR8R9, CH2N+R8R9R10 Z-; R1, R2, R4 = independently H, OH; R3 = H, OH, C1-4 alkoxy, PhCH2O; R5 = H; R6 = H, Me; R7 = C9-21 alkyl, C9-21 alkenyl, C1-10 alkoxyphenyl, C1-10 alkoxynaphthyl; R8, R9 = independently H, C1-4 alkyl, CH2Ph; R10 = C1-4 alkyl; R8R9 = (CH2)4-6; Z- = anion of a pharmaceutically acceptable salt] and pharmaceutically acceptable salts and compns. were prepared as extremely active antibiotics. Thus, dehydration of 2.08 g carboxamide I [R = CONH2, R1 = R2 = R3 = R4 = OH, R5 = H, R6 = Me, R7 = (CH2)8CHMeCH2CHMeEt] with 550 mg. cyanuric chloride in DMF in the presence of 4Å. mol. sieves gave 880 mg nitrile I (R = CN, R1-7 = same). Reduction of 210 mg nitrile I (R = CN) with 151 mg NaBH4, and 104 mg CoCl2.6H2O in 6 mL MeOH gave 110 mg I (R = CH2NH2) (II) as an AcOH addition salt after chromatog. II showed activity against a variety of Candida and Cryptococcus organisms. It was also 99% effective in reducing Pneumocystis carinii cysts in rats when dosed at 0.300 mg/kg.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:521532 BIOSIS
DOCUMENT NUMBER: PREV199900521532
TITLE: **Cyclohexapeptidyl propanolamine**

cyclohexypeptide-1

compounds.
AUTHOR(S): Balkovec, James M. [Inventor, Reprint author]; Hammond, Milton L. [Inventor]; Zambias, Robert A. [Inventor]
CORPORATE SOURCE: North Plainfield, NJ, USA
ASSIGNEE: Merck and Co., Inc.
PATENT INFORMATION: US 5948753 Sep. 07, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 7, 1999) Vol. 1226, No. 1. print.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 1999
Last Updated on STN: 3 Dec 1999

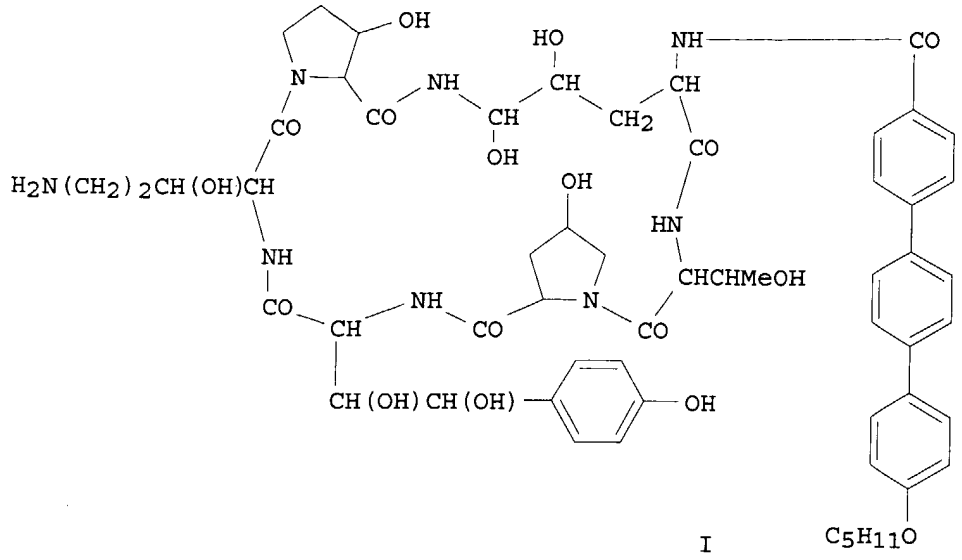
L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:340888 CAPLUS
DOCUMENT NUMBER: 122:299077
TITLE: Preparation and pharmaceutical compositions of **cyclohexapeptidyl propanolamine** compounds for antibiotics
INVENTOR(S): Balkovec, James M.; Hammond, Milton L.; Zambias, Robert A.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9425050	A1	19941110	WO 1994-US4169	19940415
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5948753	A	19990907	US 1993-58657	19930504
CA 2161150	AA	19941110	CA 1994-2161150	19940415
AU 9469033	A1	19941121	AU 1994-69033	19940415
AU 670384	B2	19960711		
EP 701447	A1	19960320	EP 1994-917261	19940415
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08509728	T2	19961015	JP 1994-524337	19940415

PRIORITY APPLN. INFO.: US 1993-58657 A 19930504
WO 1994-US4169 W 19940415

OTHER SOURCE(S): MARPAT 122:299077
GI

cyclohexypeptide-1



I

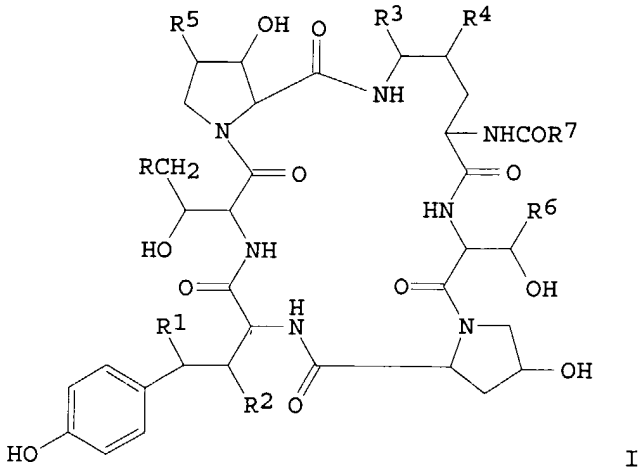
AB **Propanolamine** compds. having a **cyclohexapeptidyl** nucleus (Markush included) and possessing antibiotic activity with phys. properties suitable for direct use in therapeutic compns. are disclosed. A novel process for their preparation is also described. Four such compds. ,e.g. I, are specifically claimed. Tablet, capsule, aerosol, and injection formulations are presented. The compds. of the invention are especially useful for treatment of mycotic infections and are also useful for prevention and treatment of Pneumocystis carinii pneumonia.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:581245 CAPLUS
DOCUMENT NUMBER: 119:181245
TITLE: Preparation of **cyclohexapeptidyl** **propanolamine** compounds as antibiotics
INVENTOR(S): Hammond, Milton L.; Zambias, Robert A.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 37 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 535959	A1	19930407	EP 1992-308974	19921001
EP 535959	B1	19970115		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5939384	A	19990817	US 1992-936561	19920903

PRIORITY APPLN. INFO.: US 1991-771017 A 19911001
US 1992-936561 A 19920903
OTHER SOURCE(S): MARPAT 119:181245
GI

cyclohexypeptide-1



I

AB Title compds. I [R = CH2NR8R9, CH2N+R8R9R10 Z-; R1, R2, R4 = independently H, OH; R3 = H, OH, C1-C4 alkoxy, PhCH2O; R5 = H, OH, Me; R6 = H, Me; R7 = C9-C11 alkyl, C9-C21 alkenyl, C1-C10 alkoxyphenyl, C1-C10 alkoxynaphthyl; R8, R9, R10 = independently H, C1-C4 alkyl, CH2Ph; R9R10 = (CH2)4, (CH2)5; Z- = anion of a pharmaceutically acceptable salt] and pharmaceutically acceptable salts and compns. were prepared as extremely active antibiotics. Thus, dehydration of 2.08 g carboxamide I [R = CONH2, R1 = R2 = R3 = R4 = OH, R5 = H, R6 = Me, R7 = (CH2)8CHMeCH2CHMeEt] with 550 mg. cyanuric chloride in DMF in the presence of 4Å mol. sieves gave 880 mg nitrile I (R = CN, R1-7 = same). Reduction of 210 mg nitrile I (R = CN) with 151 mg NaBH4, and 104 mg CoCl2.6H2O in 6 mL MeOH gave 110 mg I (R = CH2NH2) (II) as an AcOH addition salt after chromatog. II showed activity against a variety of Candida and Cryptococcus organisms.

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=> d his

     (FILE 'HOME' ENTERED AT 14:07:02 ON 11 JUN 2004)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     14:07:30 ON 11 JUN 2004
L1          2429 S CYCLIC (P) HEXAPEPTIDE
L2           432 S CYCLOHEXAPEPTID?
L3          2707 S L1 OR L2
L4          9770 S PROPANOLAMINE
L5             5 S L3 (P) L4
L6             4 DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)

=> s infectious disease
L7       123610 INFECTIOUS DISEASE

=> s antimicrobial or antifungal or microorganism
L8      3149723 ANTIMICROBIAL OR ANTIFUNGAL OR MICROORGANISM

=> s l3 (p) l7 (p) l8
L9             0 L3 (P) L7 (P) L8

=> s l3 (p) (l7 or l8)
L10          101 L3 (P) (L7 OR L8)

=> s l10 (p) l4
L11            1 L10 (P) L4
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cyclohexypeptide-1

=> s l11 not l6
L12 0 L11 NOT L6

=> s kit or article or package
L13 5348646 KIT OR ARTICLE OR PACKAGE

=> s l13 (p) l3
L14 8 L13 (P) L3

=> duplicate remove l14
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L14
L15 5 DUPLICATE REMOVE L14 (3 DUPLICATES REMOVED)

=> s l15 (p) l4
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L104 (P) L24'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L108 (P) L26'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L110 (P) L27'
L16 0 L15 (P) L4

=> d l15 1-5 ibib abs

L15 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:317682 CAPLUS
TITLE: Synthesis of azine-type heterocyclic compoundsand their conversion into functional molecules
AUTHOR(S): Katoh, Akira; Saito, Ryota
CORPORATE SOURCE: Dep. of Engineering, Seikei University, Musashino-shi, Tokyo, 180-8633, Japan
SOURCE: Yuki Gosei Kagaku Kyokaishi (2004), 62(4), 335-346
CODEN: YGKKAE; ISSN: 0037-9980
PUBLISHER: Yuki Gosei Kagaku Kyokai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB We have focused on the synthesis of azine-type heterocyclic compds. and their conversion into useful functional mols. In this **article**, the following points were reviewed. 1) 6-Amino-2, 3-dimorpholinoquinoxalines bearing the amino acid residues at C-6 position were found to be highly-sensitive fluorescent chiral derivatization reagents. 2) A new tripodal heterocyclic hexadentate ligand, in which three sets of 3-hydroxy-4(1H)-pyridinone and ethyleneoxy chain are linked to tris(carboxyethoxymethyl)ethane was synthesized. The allosteric binding of alkali metal ions to a pseudocryptand formed by the ligand and Ga(mI) was discussed. 3) Hydroxyazine-type linear and **cyclic hexapeptides** were newly synthesized. The iron(M) complex-forming tendency, the absolute configuration, the stability constant, the iron(M) removal from human transferrin, and the growth-promotion activity were discussed. 4) Oxovanadium complexes of 3-hydroxy-4(1H)-pyridinones were synthesized. The spectroscopic characterization of the complexes was carried out on the basis of 1H-, 51V-NMR, IR, UV-VIS, FAB MS, ESI MS and ESR spectra, and **cyclic** voltammetry (CV). Further, an extremely high insulin-mimetic activity of bis(1,4-dihydro-2-methyl-1-phenyl-4-thioxo-3-pyridinolato)zinc(II) complex was also discussed.

L15 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:28430 CAPLUS
TITLE: Conformational properties of cyclic peptides containing 2-aminocycloalkane carboxylic acids

cyclohexypeptide-1

AUTHOR(S): Strijowski, U.; Sewald, N.
CORPORATE SOURCE: Department of Chemistry, University of Bielefeld, Bielefeld, D-33501, Germany
SOURCE: Peptides 2002, Proceedings of the European Peptide Symposium, 27th, Sorrento, Italy, Aug. 31-Sept. 6, 2002 (2002), 288-289. Editor(s): Benedetti, Ettore; Pedone, Carlo. Edizioni Ziino: Castellammare di Stabia, Italy.
CODEN: 69EYXG; ISBN: 88-900948-1-8
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A number of 2-aminocycloalkane carboxylic acids (ACAC) were synthesized and were used as mimics for proline in a series of **cyclic** penta- and **hexapeptides** containing parts of a binding epitope of VCAM-1. Peptides were synthesized with Fmoc/tBu/trityl protection on 2-chloro trityl resin with TBTU/DIPEA on an Advanced ChemTech 496 MOS. The synthesized peptides have the sequence c-(Ser-ACAC-Leu-Asp-Asn-) and c-(Ser-ACAC-Leu-Asp-Ile-Asn-) with different proline mimetics. The interproton distances have been used as restraints for mol. modeling using the GROMACS **package.**

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1999203772 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10101224
TITLE: 2-pyridylthioureas: novel nonpeptide somatostatin agonists with SST4 selectivity.
AUTHOR: Liu S; Crider A M; Tang C; Ho B; Ankersen M; Stidsen C E
CORPORATE SOURCE: Division of Basic Pharmaceutical Sciences, School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209-0470, USA.
SOURCE: Current pharmaceutical design, (1999 Apr) 5 (4) 255-63. Ref: 59
Journal code: 9602487. ISSN: 1381-6128.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990608

AB Somatostatin [somatotropin release-inhibiting factor (SRIF)] is a **cyclic** tetradecapeptide that is a potent inhibitor of growth hormone (GH) secretion from the anterior pituitary. In addition to the inhibitory effects on GH-release, SRIF-14 and SRIF-28, a 28-amino acid form of SRIF extended from the N-terminal end, inhibit the release of a variety of other peptides including glucagon, insulin, and gastrin, and both peptides act as neurotransmitters and neuromodulators in the central nervous system and the periphery. SRIF exerts its potent inhibitory effects following binding to high affinity SRIF receptors (ssts) that have been identified on target tissues. The recent cloning of five ssts has confirmed that the effects of SRIF are mediated by a family of G protein-coupled receptors (sst1-5). Based on structural and pharmacological properties sst2, sst3, and sst5 belong to the SRIF1 receptor subclass, and the sst1 and sst4 subtypes comprise the SRIF2 subclass. The major difference between these two subclasses is that SRIF1 receptors bind octapeptide and **hexapeptide** SRIF-14 analogs with high affinity, while SRIF2 receptors bind these analogs with drastically reduced affinity. A screening program was initiated to identify a lead

nonpeptide with affinity for sst1-5 receptors. The search focused on a scaffold with the following attachments: (1) a heteroaromatic nucleus to mimic the Trp8 residue, (2) a nonheteroaromatic nucleus to mimic Phe7, and (3) a primary amine or other basic group to mimic the Lys9 residue of SRIF-14. Using these criteria, a novel thiourea (NNC 26-9100, 17) was discovered as a structural lead. The key fragments in this compound are a heteroaromatic moiety (pyridine), an aromatic group, and a basic imidazole group connected through a thiourea scaffold. Compound 17 exhibited a Ki = 6 nM at sst4 receptors with a 100-fold sst4/sst2 selectivity and was shown to be a full agonist at this receptor subtype. This **article** will review the literature on the design and development of nonpeptide somatostatin receptor ligands and the therapeutic potential of these agents. Furthermore, our work on the development of 2-pyridylthioureas as sst4 receptor agonists will be described.

L15 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:637325 CAPLUS
DOCUMENT NUMBER: 130:34771
TITLE: Mimicking extended conformations of protease substrates: designing cyclic peptidomimetics to inhibit HIV-1 protease
AUTHOR(S): Reid, Robert C.; Fairlie, David P.
CORPORATE SOURCE: Centre for Drug Design and Development, University of Queensland, Brisbane, Australia
SOURCE: Advances in Amino Acid Mimetics and Peptidomimetics (1997), 1, 77-107
CODEN: AAAMF9
PUBLISHER: JAI Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 55 refs. There are many examples of structurally distinct **cyclic** peptides that potently regulate biol. processes (e.g. Curr. Med. Chemical 1995, 2, 654-686), but the method of altering their structures to obtain optimal bioactivity is still largely trial and error and thus is painstakingly slow. In this **article** we describe a more rational approach to inhibitor design that focuses on directly mimicking the conformations of peptidic substrate analogs that bind to the protease of Human Immunodeficiency Virus type 1 (HIVPR). This application of inhibitor design to the specific example of HIVPR is illustrative of a general approach to the structural mimicry of receptor-binding conformations of substrates for other proteases. The macrocycles are easily synthesized, conformationally rigid, proteolytically stable, water and lipid soluble, and can be readily varied by altering the size or substituents of a cycle. Such mols. promise to be important mechanistic probes of biol. processes and potential drug leads. A novel hypothesis that extended (strand) substrate conformations are selectively recognized by proteolytic enzymes in general is demonstrated here for HIV-1 protease and supported by our evidence elsewhere for this and other proteases. Evidence includes (1) a consensus extended conformation in X-ray crystal structures of all substrate-mimicking peptidic inhibitors bound to HIV-1 protease, (2) slower processing for turn- or helix-favoring peptide substrates, (3) lack of turn/helical/sheet structure in peptide and also protein substrates that are most rapidly degraded by HIV-1 protease, and (4) factors that promote stretching of the amide bond for substrate processing. Based upon this apparent conformational selection by HIV-1 protease of peptides and analogs in extended strand conformations, we have designed macrocycles that constrain segments of peptide sequences to an extended conformation. These include **cyclic** replacements for N-terminal tri- and tetra-peptides, C-terminal tri- and tetra-peptides, and bicyclic **hexapeptide** analogs which replace both ends. X-ray crystal structures show that these are all structural mimics of protease-binding conformations of substrate analogs. Mol. modeling and NMR spectroscopic studies identify the extent of conformational

restriction afforded by the macrocycles. This structural mimicry leads to functional mimicry, since the **cyclic** compds. selectively inhibit HIV-1 protease at nanomolar concns. when attached to appropriate peptidic and non-peptidic appendages. Unlike acyclic peptide analogs which do not inhibit HIV-1 replication in cells, these macrocycles are pre-organized for receptor-binding, less conformationally flexible than acyclic components of peptidomimetic inhibitors, more resistant to proteolysis than their acyclic analogs, and lipophilic enough to penetrate cell membranes for antiviral activity. This regioselective fixing of the conformation of components of inhibitors for HIV-1 protease may also be useful in designing structural and functional peptidomimetics for substrates of other proteolytic enzymes. The design, synthesis, structure and activities of inhibitors of HIV-1 protease are now described, focusing on some of our work toward incorporating cycles into peptidomimetics.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 5 EMBASE
on STN

ACCESSION NUMBER: 95234621 EMBASE
DOCUMENT NUMBER: 1995234621
TITLE: Echinocandin lipopeptide antifungal agents: New agents and recent chemical modification studies.
AUTHOR: Debono M.
CORPORATE SOURCE: Eli Lilly and Company Inc., Lilly Corporate Center,Indianapolis, IN 46285, United States
SOURCE: Expert Opinion on Therapeutic Patents, (1995) 5/8 (771-786).
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The search for new and effective antifungal agents has been intensified by the increase in the incidence of opportunistic infections due to immunological diseases and aggressive immunosuppressive chemotherapy. Natural products have provided several novel leads in this field. Of these the echinocandin lipopeptides are of special interest due to their fungicidal properties and low toxicity. Their mode of action uniquely targets fungal cell wall biosynthesis by inhibiting the production of β-(1,3)-D-glucan, an essential cell wall component. Echinocandin B (ECB) consists of a **cyclic hexapeptide** whose N-terminus is acylated with linoleic acid. Other natural products of this class have closely related structures with some modification of the **cyclic** peptide and/or the N-acyl fatty acid chain. Although these natural products share excellent antifungal activity, especially against Candida albicans, and low toxicity, further improvements in therapeutic and solubility properties were sought through chemical modification. Major efforts have been ongoing at both Merck and Lilly in the quest for natural and semisynthetic echinocandin lipopeptides which will provide novel clinical candidates with a unique mode of action. This **article** describes the development of this class of compounds by reviewing both the primary and patent literature.

=> d his

(FILE 'HOME' ENTERED AT 14:07:02 ON 11 JUN 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:07:30 ON 11 JUN 2004

cyclohexypeptide-1

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L1          2429 S CYCLIC (P) HEXAPEPTIDE
L2           432 S CYCLOHEXAPEPTID?
L3          2707 S L1 OR L2
L4          9770 S PROPANOLAMINE
L5             5 S L3 (P) L4
L6             4 DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)
L7        123610 S INFECTIOUS DISEASE
L8       3149723 S ANTIMICROBIAL OR ANTIFUNGAL OR MICROORGANISM
L9             0 S L3 (P) L7 (P) L8
L10          101 S L3 (P) (L7 OR L8)
L11            1 S L10 (P) L4
L12            0 S L11 NOT L6
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L14            8 S L13 (P) L3
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L16            0 S L15 (P) L4

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L17          752 TODA A?/AU

=> s matsuya t?/au
L18          580 MATSUYA T?/AU

=> s mizuno h?/au
L19         3570 MIZUNO H?/AU

=> s matsuda h?/au
L20        17535 MATSUDA H?/AU

=> s murano k?/au
L21          477 MURANO K?/AU

=> s barrett d?/au
L22         3082 BARRETT D?/AU

=> s ogino t?/au
L23         3263 OGINO T?/AU

=> s matsuda k?/au
L24         9411 MATSUDA K?/AU

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=> s l25 and l3
L26            4 L25 AND L3

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DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L26
L27            4 DUPLICATE REMOVE L26 (0 DUPLICATES REMOVED)

=> d l27 1-4 ibib abs

L27  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2001:618024  CAPLUS
DOCUMENT NUMBER:          135:180954
TITLE:                    Synthesis of cyclic hexapeptide
                          derivatives for use as antimicrobial or antifungal
                          agents in humans or animals
INVENTOR(S):              Toda, Ayako; Matsuya, Takahiro;
                          Mizuno, Hiroaki; Matsuda, Hiroshi;
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cyclohexypeptide-1

Murano, Kenji; Barrett, David;
Ogino, Takashi; Matsuda, Keiji

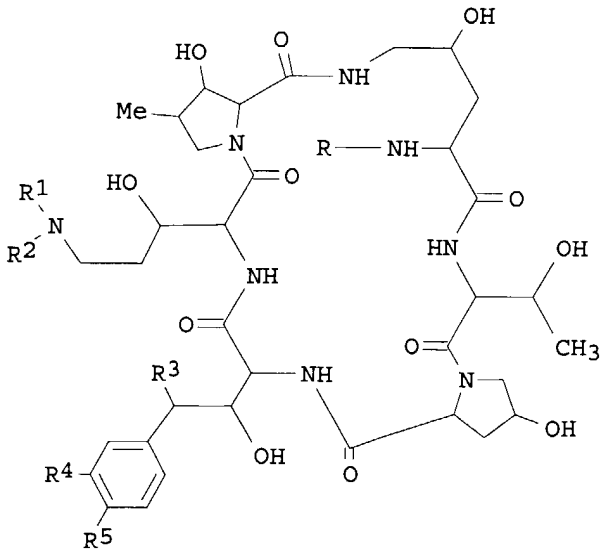
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060846	A1	20010823	WO 2001-JP1204	20010220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001034095	A5	20010827	AU 2001-34095	20010220
EP 1259535	A1	20021127	EP 2001-906140	20010220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001008792	A	20021203	BR 2001-8792	20010220
JP 2003523349	T2	20030805	JP 2001-560230	20010220
RU 2224765	C1	20040227	RU 2002-125463	20010220
NZ 520808	A	20040326	NZ 2001-520808	20010220
US 2003083238	A1	20030501	US 2002-30161	20020130
NO 2002003697	A	20021014	NO 2002-3697	20020806

PRIORITY APPLN. INFO.:
AU 2000-5752 A 20000221
AU 2000-9552 A 20000821
AU 2000-2344 A 20001228
WO 2001-JP1204 W 20010220

OTHER SOURCE(S): MARPAT 135:180954

GI



I

cyclohexypeptide-1

AB Cyclic polypeptides [(I); R, R1 (independently) = H, acyl; R2 = hydroxyalkyl; R3 = H, OH; R4 = H, OH, alkoxy, HO3SO-; R5 = OH, acyloxy], useful as antimicrobial or antifungal agents, or as β-1,3-glucan synthase inhibitors (no data), for use in prophylactic and/or therapeutic treatment of infectious diseases in humans or animals, were prepared A variety of substituted acyl R groups were prepared and coupled with the cyclopeptide. Thus, I [R = 4-[2-[4-[4-[5-methoxypentyloxy]piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]phenylcarbonyl; R1,R3 = H; R2 = CH(CH2OH)2; R4 = HO3SO; R5 = OH (II)] was prepared in four steps from the starting protected cyclic peptide sodium salt and activated ester of substituted benzoic acid (preparation given). In in vitro tests of antimicrobial activity in mouse serum against Candida albicans FP-633, II had MIC <0.3 μg/mL.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:510397 BIOSIS
DOCUMENT NUMBER: PREV200100510397
TITLE: **Cyclic hexapeptides** with antimicrobial activity.
AUTHOR(S): Ohki, Hidenori [Inventor, Reprint author]; **Murano, Kenji** [Inventor]; Tojo, Takashi [Inventor]; Shiraishi, Nobuyuki [Inventor]; **Matsuya, Takahiro** [Inventor]; **Matsuda, Hiroshi** [Inventor]; **Mizuno, Hiroaki** [Inventor]; **Barrett, David** [Inventor]; **Matsuda, Keiji** [Inventor]; Kawabata, Kohji [Inventor]
CORPORATE SOURCE: Takarazuka, Japan
ASSIGNEE: Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan
PATENT INFORMATION: US 6232290 May 15, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 15, 2001) Vol. 1246, No. 3. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Oct 2001
Last Updated on STN: 23 Feb 2002

AB This invention relates to new polypeptide compounds represented by general formula (I), wherein R1, R2, R3 and R4 are as defined in the description or a salt thereof which has antimicrobial activities (especially, antifungal activities), inhibitory activity on beta-1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal. ##STR1##

L27 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:772658 CAPLUS
DOCUMENT NUMBER: 133:335462
TITLE: Preparation of **cyclic hexapeptides** having antibiotic activity
INVENTOR(S): Tojo, Takashi; Ohki, Hidenori; Shiraishi, Nobuyuki; **Matsuya, Takahiro**; **Matsuda, Hiroshi**; **Murano, Kenji**; **Barrett, David**; **Ogino, Takashi**; **Matsuda, Keiji**; Ichihara, Masaharu; Hashimoto, Norio; Kanda, Atsushi; Ohigashi, Atsushi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 449 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

cyclohexypeptide-1

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064927	A1	20001102	WO 2000-JP2710	20000425
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1173472	A1	20020123	EP 2000-917469	20000425
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003501347	T2	20030114	JP 2000-614276	20000425

PRIORITY APPLN. INFO.: AU 1999-9997 A 19990427
WO 2000-JP2710 W 20000425
OTHER SOURCE(S): MARPAT 133:335462
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB **Cyclic hexapeptides** I [R1 = H, acyl; R2, R3 = H, cyano, (un)substituted alkyl, acyl, heterocyclyl, alkylidenyl; R4 = H, OH; R5 = H, OH, alkoxy, hydroxysulfonyloxy; R6 = OH, acyloxy] or their salts were prepared for use as antimicrobials, especially fungicides. Thus, **cyclic** peptide II [R1 = p-[5-[4'-(2-methoxyethoxy)[1,1'-biphenyl]-4-yl]thiazol-2-yl]benzoyl], prepared via N-acylation reaction, showed MIC <0.3 μg/mL for inhibition of Candida albicans.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:511176 CAPLUS
DOCUMENT NUMBER: 131:144853
TITLE: **Cyclic hexapeptides** having antimicrobial activity
INVENTOR(S): Ohki, Hidenori; **Murano, Kenji**; Tojo, Takashi; Shiraishi, Nobuyuki; **Matsuya, Takahiro**; **Matsuda, Hiroshi**; **Mizuno, Hiroaki**; **Barrett, David**; **Matsuda, Keiji**; Kawabata, Kohji
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; et al.
SOURCE: PCT Int. Appl., 470 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940108	A1	19990812	WO 1999-JP538	19990205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

cyclohexypeptide-1

CA 2320416	AA	19990812	CA 1999-2320416	19990205	
AU 9922998	A1	19990823	AU 1999-22998	19990205	
AU 756792	B2	20030123			
BR 9907967	A	20001017	BR 1999-7967	19990205	
EP 1053247	A1	20001122	EP 1999-902855	19990205	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
TR 200003064	T2	20010221	TR 2000-20000306	19990205	
JP 2001522377	T2	20011113	JP 1999-540287	19990205	
RU 2219185	C2	20031220	RU 2000-123404	19990205	
ZA 9900985	A	19990810	ZA 1999-985	19990208	
US 6232290	B1	20010515	US 1999-446101	19991222	
NO 2000003996	A	20001009	NO 2000-3996	20000808	
JP 2004067699	A2	20040304	JP 2003-322336	20030912	

PRIORITY APPLN. INFO.:	AU 1998-1728	A	19980209	
	AU 1998-3138	A	19980423	
	JP 1999-540287	A3	19990205	
	WO 1999-JP538	W	19990205	

OTHER SOURCE(S): MARPAT 131:144853
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Polypeptides I [R1 = H, (un)substituted arylaminoalkanoyl, aroyl, arylalkanoyl, or alkanoyl, amino protective group, heptylnaphthoyl, hexylnaphthoyl; R2 = H, OH; R3 = OH, hydroxysulfonyloxy, alkoxy; R4 = OH, alkoxy] or their salts were prepared as antimicrobial activities (especially, antifungal activities). Thus, cyclic peptide II, prepared via N-acylation using 4-[5-[4-(6-methoxyhexyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester, showed MIC 0.0625 μg/mL for inhibition of Candida albicans.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 14:07:02 ON 11 JUN 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:07:30 ON 11 JUN 2004

L1	2429	S CYCLIC (P) HEXAPEPTIDE
L2	432	S CYCLOHEXAPEPTID?
L3	2707	S L1 OR L2
L4	9770	S PROPANOLAMINE
L5	5	S L3 (P) L4
L6	4	DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)
L7	123610	S INFECTIOUS DISEASE
L8	3149723	S ANTIMICROBIAL OR ANTIFUNGAL OR MICROORGANISM
L9	0	S L3 (P) L7 (P) L8
L10	101	S L3 (P) (L7 OR L8)
L11	1	S L10 (P) L4
L12	0	S L11 NOT L6
L13	5348646	S KIT OR ARTICLE OR PACKAGE
L14	8	S L13 (P) L3
L15	5	DUPLICATE REMOVE L14 (3 DUPLICATES REMOVED)
L16	0	S L15 (P) L4
L17	752	S TODA A?/AU
L18	580	S MATSUYA T?/AU
L19	3570	S MIZUNO H?/AU
L20	17535	S MATSUDA H?/AU

cyclohexypeptide-1

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L21          477 S MURANO K?/AU
L22         3082 S BARRETT D?/AU
L23         3263 S OGINO T?/AU
L24         9411 S MATSUDA K?/AU
L25        38544 S L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23   OR L24
L26            4 S L25 AND L3
L27            4 DUPLICATE REMOVE L26 (0 DUPLICATES REMOVED)

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    78.84      79.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -6.24      -6.24

STN INTERNATIONAL LOGOFF AT 14:17:02 ON 11 JUN 2004
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	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	541	cyclic same hexapeptide	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:43			0
2	BRS	L2	121	cyclohexapeptid$2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:43			0
3	BRS	L3	647	1 or 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:43			0
4	BRS	L4	3057	propanolamine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:44			0
5	BRS	L5	10	3 same 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:53			0
6	BRS	L6	26192	infectious adj disease	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:53			0
7	BRS	L7	212601	microorganism or antimicrobial or antifungal	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:54			0
8	BRS	L8	65	3 same (6 or 7)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:55			0
9	BRS	L9	0	8 same 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:55			0
10	BRS	L10	0	5 same (6 or 7)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:55			0
11	BRS	L11	1272718	kit or package or article	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:57			0
12	BRS	L12	0	5 same 11	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:57			0
13	BRS	L14	3	toda adj ayako.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:58			0
14	BRS	L15	5	matsuya adj takahiro.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:58			0
15	BRS	L16	154	mizuno adj hiroaki.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:59			0
16	BRS	L17	1614	matsuda adj hiroshi.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 13:59			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
17	BRS	L18	16	murano adj kenji.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:00			0
18	BRS	L19	134	barrett adj david.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:00			0
19	BRS	L20	188	ogino adj takashi.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:01			0
20	BRS	L21	109	matsuda adj keiji.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:01			0
21	BRS	L22	2185	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:02			0
22	BRS	L23	2	22 and 3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/06/11 14:02			0

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(FILE 'HOME' ENTERED AT 14:07:02 ON 11 JUN 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
14:07:30 ON 11 JUN 2004

L1 2429 S CYCLIC (P) HEXAPEPTIDE
L2 432 S CYCLOHEXAPEPTID?
L3 2707 S L1 OR L2
L4 9770 S PROPANOLAMINE
L5 5 S L3 (P) L4
L6 4 DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)
L7 123610 S INFECTIOUS DISEASE
L8 3149723 S ANTIMICROBIAL OR ANTIFUNGAL OR MICROORGANISM
L9 0 S L3 (P) L7 (P) L8
L10 101 S L3 (P) (L7 OR L8)
L11 1 S L10 (P) L4
L12 0 S L11 NOT L6
L13 5348646 S KIT OR ARTICLE OR PACKAGE
L14 8 S L13 (P) L3
L15 5 DUPLICATE REMOVE L14 (3 DUPLICATES REMOVED)
L16 0 S L15 (P) L4
L17 752 S TODA A?/AU
L18 580 S MATSUYA T?/AU
L19 3570 S MIZUNO H?/AU
L20 17535 S MATSUDA H?/AU
L21 477 S MURANO K?/AU
L22 3082 S BARRETT D?/AU
L23 3263 S OGINO T?/AU
L24 9411 S MATSUDA K?/AU
L25 38544 S L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24
L26 4 S L25 AND L3
L27 4 DUPLICATE REMOVE L26 (0 DUPLICATES REMOVED)

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